Protocol abstract

Title

Dulaglutide Modified Prescription-Event Monitoring and network database study: a multi- database collaborative research program of observational studies to monitor the utilisation and safety of dulaglutide in the European Union (EU).

Rationale and background

Dulaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated for the treatment of patients with type 2 diabetes mellitus (T2DM). This targeted surveillance study will be conducted in order to monitor the occurrence of certain medical conditions in patients using dulaglutide in the EU. The study will quantify the occurrence and describe the characteristics of these conditions during the first 12 months after starting dulaglutide. The conditions being monitored include acute pancreatitis, hypersensitivity, pancreatic and thyroid cancers, cardiac conduction abnormalities, gastrointestinal effects, and medication errors. Additionally, for subpopulations receiving dulaglutide where safety data are usually classified as "missing information," the distribution of these medical conditions will be described to determine if there are any differences compared to what is known for the target population. In order to assess the safety profile and utilisation of dulaglutide in the EU, a multi-database post-authorisation safety study (PASS) program will be administered by the DSRU. The DSRU will conduct a Modified Prescription-Event Monitoring (M-PEM) study in England, and it will coordinate a multi-country collaborative research program to address common aims and objectives, using existing data from three European electronic health record (EHR) databases. Each country will independently conduct an observational study developed in accordance with aims and objectives from an agreed base protocol.

Research question and objectives

The overall aim of this multi-database PASS program is to assess and understand the utilisation and safety profile of dulaglutide in patients with T2DM. Study objectives are summarised below.

The primary objective for each country is:

To estimate the cumulative incidence in the first 12 months of treatment with dulaglutide of the following events of interest:

(a) Acute pancreatitis

(b) Hypersensitivity [including anaphylaxis, and injection-site reactions]

(c) Cardiovascular (CV) events (heart rate/rhythm [supraventricular arrhythmias/tachycardia] and conduction abnormalities [atrioventricular (AV) block])

(d) Gastrointestinal (GI) effects [including GI stenosis, GI obstruction, and delayed gastric emptying]

(e) Medication errors [frequency of administration > once weekly]

The secondary objectives for each country are:

(a) To describe the baseline health profile of patients on treatment with dulaglutide and the antidiabetic treatment they received, to advance the understanding of the dulaglutide patient population in actual clinical practice.

(b) To explore time to onset of primary outcomes of interest and to explore predictors of risk in patients treated with dulaglutide.

(c) To describe the safety profile in sub-populations receiving dulaglutide which have been classified as missing information in the EU Risk Management Plan (RMP):

- children and adolescents <18 years of age
- patients >=75 years of age
- pregnant and/or breastfeeding women
- patients with hepatic impairment
- patients with severe renal failure
- patients with heart failure
- patients with severe GI disease

(d) To estimate the period prevalence of pancreatic and/or thyroid cancer in patients receiving dulaglutide during first 12 months after initial treatment.

Further objectives relating to the M-PEM study are:

(a) To describe the risk profile and characteristics of patients who experienced pancreatic cancer and/or thyroid neoplasm.

(b) Where possible, to quantify the incidence of other frequently and rarely reported events, (including hypoglycaemia, other GI effects and other important identified and potential risks not mentioned in the primary objective).

Study design

This PASS program proposes to utilise data from multiple EU countries and databases using protocols with an overall common approach. The common study design will be a single exposure retrospective observational cohort design.

Population

The study population will consist of new user patients with T2DM who were prescribed dulaglutide in the EU.

Variables

Demographic data on patients (age and sex), indication, selected treatment details, selected medical history and medication use prior to or present on start of dulaglutide treatment (index date), clinical events of medical interest.

Data sources

Data will be derived from an M-PEM study in England (Appendix 1), United Kingdom (UK) and multiple large population-based healthcare and administrative databases in the EU, including PHARMO Database Network in the Netherlands, the German Pharmacoepidemiological Research Database in Germany, and Caserta Local Health Unit in Italy (Appendix 2, Appendix 3, and Appendix 4).

Study size

For this study, a sample size of 10000 patients (3000 patients across non-UK EU countries plus 7000 patients in the UK) is desirable in order to estimate the expected (true) cumulative incidence of acute pancreatitis of 0.1% with an acceptable level of precision.

Data analysis

Summary descriptive statistics, event risk and rate calculation and time to onset regression modelling will be used.